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Building a Better Lab Mouse— The Zebrafish

By Patricia Callahan

IN MEDICAL research labs, this is the dawning of the age of aquariums.

Edging aside the trusty laboratory mouse in certain genetics studies is the tiny zebrafish, a fixture of pet stores and family fishbowls. Researchers are using the striped creature to reveal secrets of diseases of the heart, brain and aorta, as well as leukemia, muscular dystrophy and visual and hearing disorders.

The 1½-inch zebrafish costs less than a lab mouse and reproduces prolifically, spawning about 2,000 progeny a year, compared with about 45 offspring for a mouse. The zebrafish, which takes up less space in labs, costs about $7 a year to keep, compared with $90 a year to maintain a mouse.

For gene research, the zebrafish is less costly and easier to use than mice. It's more colorful, too.

Best of all, unlike a mouse, a female zebrafish lays eggs, which are fertilized outside her body. Because the embryos develop outside their mothers, researchers easily can observe and manipulate them as they grow.

By contrast, the mouse, which is a mammal, develops inside its mother's womb. Researchers who want to see the mouse embryo at a particular stage of development must kill it and its mother. "You get only snapshots rather than the whole process," says P. Paul Liu, a senior investigator at the National Human Genome Research Institute in Bethesda, Md. Dr. Liu, a leukemia researcher, added zebrafish to his mouse lab to study genes that lead to the formation of blood in embryos.

Another bonus: Zebrafish embryos are nearly transparent in their early stages of development. That means scientists can easily spot mutations at work as the cells divide and the embryo develops.

But not everyone applauds the use of the fish in research. People for the Ethical Treatment of Animals, which has long fought the use of monkeys, mice and other mammals in research, also opposes the use of zebrafish. "Even though there is a perception that fish are a so-called lower species, we don't buy that," says Troy Seidle, a science policy adviser for the organization.

The late George Streisinger, a genetics researcher at the University of Oregon, is widely credited with developing the zebrafish, native to the Ganges River in India, as a laboratory creature. For years, Dr. Streisinger faced skepticism as he pioneered use of the zebrafish (*Rerio danio*) for genetics studies in the 1970s. But

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The New Lab Rat Has Gills, Stripes: It's the Zebrafish

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today, Dr. Streisinger, who died during a scuba-diving class in 1984, is considered a visionary.

The National Institutes of Health this fall plans to begin building a $17.5 million zebrafish facility to house as many as 500,000 of the cold-blooded creatures in 25,000 1 and 2-liter tanks.

Since Dr. Liu added zebrafish to his leukemia research at the National Institutes of Health four years ago, two more researchers have followed suit, and the government institutes hired two new zebrafish researchers, doubling to eight the number of zebrafish labs.

When Alvin Chin, a pediatrics professor at the University of Pennsylvania School of Medicine in Philadelphia, took a sabbatical to do genetics research with zebrafish in 1991, colleagues urged him to go to a mouse lab instead. "They thought I was crazy," says Dr. Chin, who now runs his own zebrafish lab. "Now I don't think anyone disputes that information you find from zebrafish mutation will be relevant to human disease."

While zebrafish can swim circles around mice in some ways, the mouse is superior in others. As mammals, mice are more similar to humans—scientists estimate that humans diverged from mice on the evolutionary ladder 75 million to 80 million years ago—and mice have been studied for about a century. Zebrafish are believed to have diverged from humans as far back as about 450 million years ago, yet researchers have noted a remarkable similarity between human and zebrafish genes. Often zebrafish and mice are used to complement one another; geneticists may start with zebrafish and move on to mice.

Notably, mouse researchers have developed a way to target a specific gene and knock out only that gene's function. That way they don't have to force mutations in thousands of animals to find the genetic abnormality they want.

That can't be done yet in zebrafish, but the race is on. Researchers at Purdue University, West Lafayette, Ind., last week said they received a $1 million three-year National Institutes of Health grant to develop a way to target zebrafish genes and turn them off permanently.

But for now, scientists usually add chemicals to force mutations in the zebrafish genes. The researchers then screen the fish and catalog them based on their abnormalities. When a gene is altered, scientists can deduce what traits that gene influences by observing the offspring of the mutant zebrafish.

Some in the pharmaceutical industry believe zebrafish research may lead to the discovery of new drugs. Mark Fishman, a cardiologist who pioneered early genetics studies of zebrafish at Massachusetts General Hospital, last year became global head of research for Novartis AG. The Swiss company's new drug-discovery research headquarters in Cambridge, Mass., now has a zebrafish lab.

The drug maker also is funding research by Randall Peterson, an assistant professor of medicine at Massachusetts General Hospital. Dr. Peterson, who worked with Dr. Fishman before he left for Novartis, puts mutated zebrafish embryos into tiny wells. Then he adds potential drugs and sees if the drugs will reverse the genetic abnormality. "You couldn't screen through thousands of potential drugs in mice," he says. "They're much too big and much too expensive."

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